Dkt. 54927-A-PCT-US/JPW/JXH

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Michael Konkel et al.

Serial No.: 09/764,710 Examiner: A. Small

Filed : January 17, 2001 Group Art Unit: 1626

For : COMPOUNDS SPECIFIC FOR THE HUMAN α_{1d} ADRENERGIC RECEPTOR AND USES THEREOF

1185 Avenue of the Americas
New York, New York 10036
December 27, 2002

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

DECLARATION OF MICHAEL KONKEL, PH.D. PURSUANT TO 37 C.F.R. §1.132

I, Michael Konkel, Ph.D. hereby declare as follows:

1. I hold a Ph.D. degree in Organic Chemistry and have worked in the field of small molecule discovery research for over 6 years. A copy of my curriculum vitae is attached hereto as **Exhibit 1**. I am currently a group leader in the Department of Medicinal Chemistry at Synaptic Pharmaceutical Corporation ("Synaptic"), the assignee of the subject patent application.

2. I have reviewed the Office Action issued by the United States Patent and Trademark Office issued on August 27, 2002, wherein the pending claims 2-4 directed to methods of inhibiting activation of a human α_{1d} adrenergic receptor with selectivity over the human α_{1b}, α_{1a} and $5HT_{1A}$ receptors were rejected as being anticipated by Wu, Y.-H. et al. Psychosedative Agents. N-(4-Phenyl-1-piperazinylalkyl)-substituted cyclic imides. *J. Med. Chem.* (1969) 12: 876-

881.

3. The subject application discloses methods of inhibiting activation of the human α_{1d} adrenergic receptor with varying degrees of selectivity over the human α_{1b}, α_{1a} and $5HT_{1A}$ receptors and compounds useful for such purposes. See, page 63, lines 3-18; and see also new claims 2-4, as amended, a copy of which is attached as **Exhibit 2.**

4. Applicant maintains that the use of compounds disclosed in Wu, et al., namely compounds 3, 11, 14, 16, 18, 21, 24, 31 and 34, do not fall within the scope of the claimed invention of claims 2-4, as amended.

5. In support of my statement made in preceding paragraph four, I submit the following:

(a) The binding affinity and selectivity profiles of compounds 3, 11, 14, 18, 24 and 25 that were determined by me or my colleagues at Synaptic according to the procedure provided in the subject application. See report entitled "Binding Affinity and Selectivity Profiles of Compounds disclosed in Wu, et al.", a copy of which is attached hereto as **Exhibit 3.**

(b) Although no data have been generated for compounds 16, 21, 31 and 34, disclosed by Wu, et al., the use of these compounds would not fall within the scope of claims 2-4, as amended. Specifically, 16 is a positional isomer of 11 and 14 from which it can be anticipated that 16 would have essentially the same binding and selectivity profile as its positional isomers, 11 and 14. Likewise, 21 is a positional isomer of 18 and 24; 31 and 34 are the positional

Michael Konkel

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Goal

Obtain a research position in a small to medium-size pharmaceutical company where my skills and creativity in organic synthesis can be utilized.

Education

Feb. 1993	University of Minnesota, Minneapolis, MN Ph. D. Chemistry, organic advisor: Wayland E. Noland
Feb. 1987	Winona State University, Winona, MN B. S. Chemistry, minor in Mathematics

Technical Experience

May 1993	Post-Doctoral Associate with Robert Vince Department of Medicinal Chemistry University of Minnesota, Minneapolis, MN
Feb. - May 1993	Post-Doctoral Associate with Wayland E. Noland Department of Chemistry University of Minnesota, Minneapolis, MN
Sept. 1987 - Feb. 1993	Research assistant at University of Minnesota, Minneapolis, MN
Feb. - Sept. 1987	Watkins Incorporated, agricultural analytical laboratory Winona, MN
June - Aug. 1986	3M Undergraduate Research Fellowship Winona State University, Winona, MN

Military

Feb. 1981 - Feb. 1983	United States Regular Army. Specialist E4. Field Artillery Surveyor. Honorable discharge.

Publications

Co-author of 9 publications in peer-reviewed journals (published or in press).

References

Available upon request

New Claims 2-4, as Amended

--2. (Amended) A method of inhibiting activation of a human α_{1d} adrenergic receptor which comprises contacting the receptor with a compound so as to inhibit activation of the receptor, wherein the compound binds to the human α_{1d} adrenergic receptor with a binding affinity which is at least 25-fold higher than the binding affinity with which the compound binds to (i) a human α_{1a} adrenergic receptor and (ii) a human α_{1b} adrenergic receptor, and the compound binds to the human α_{1d} adrenergic receptor with a binding affinity which is at least ten-fold higher than the binding affinity with which the compound binds to a human 5-HT_{1a} receptor. --

3. The method of claim 2, wherein the compound binds to the human α_{1d} adrenergic receptor with a binding affinity which is at least 25-fold higher than the binding affinity with which the compound binds to (i) a human α_{1a} adrenergic receptor, (ii) a human α_{1b} adrenergic receptor, and (iii) the human 5-HT_{1a} receptor.

4. The method of claim 3, wherein the compound binds to the human α_{1d} adrenergic receptor with a binding affinity which is at least 100-fold higher than the compound binds to (i) a human α_{1a} adrenergic receptor, (ii) a human α_{1b} adrenergic receptor, and (iii) the human 5-HT_{1a} receptor.

isomers of 25. Therefore, compounds 21, 31 and 34 would be expected to have selectivity profiles essentially the same as their respective positional isomers.

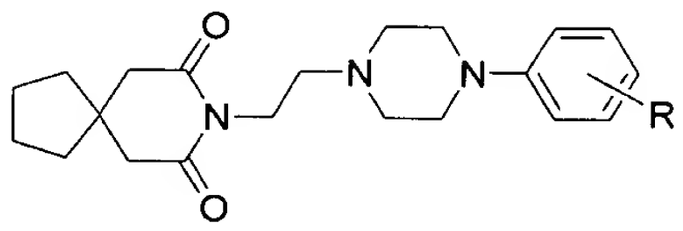
(c) According to the data in **Exhibit 3**, none of the compounds disclosed by Wu, et al. possess the selectivity required in the method claims 2-4, as amended. Specifically, the selectivity of Wu's compounds, which bind to the α1d receptor relative to the 5HT1a receptor, does not exceed 10-fold.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statements may jeopardize the validity of the application or any patent issued thereon.

12/24/02
Date

Michael Konkel, Ph.D.

Binding Affinity and Selectivity Profiles of Compounds disclosed in Wu, et al.



Binding Affinity

R	Compound No.	α_{1D} K_i (nM)	α_{1B} K_i (nM)	α_{1A} K_i (nM)	$5HT_{1A}$ K_i (nM)
H	3	6.21	1080	6261	7.30
2-CH_3	11	1.43	69.8	156	5.50
3-CH_3	14	17.1	838	1510	1.08
2-OCH_3	25	1.60	191	294	0.46
2-Cl	18	1.07	39.7	220	3.87
4-Cl	24	32.0	977	1647	170

Selectivity Ratio

α_{1B}	α_{1A}	$5HT_{1A}$
174	1008	1.17
48.8	109	3.84
49.0	88.3	0.11
119	183	0.29
37.1	206	3.61
30.5	51.4	5.32